Children's Exposure to Diagnostic Medical Radiation and Cancer Risk: An Epidemiologist's Perspective

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A 1956 report linking elevated risk of childhood cancer with prenatal abdominal diagnostic X-ray exposures of mothers was followed by numerous case–control epidemiological studies that generally confirmed increased risks of leukemia, and often other childhood malignancies, subsequent to prenatal diagnostic X-ray exposures (reviewed in ref. *1*). Intense debate about the likely causality of this association for more than 45 years has mirrored ongoing controversy about the carcinogenic risks linked with other low-dose or low-dose-rate exposure to ionizing radiation (*1–3*). The possible role of prenatal (and, to a lesser degree, preconception and postnatal) exposures to diagnostic X rays in the occurrence of childhood cancer has received extensive attention because the etiology of childhood malignancies is poorly understood, ionizing radiation at high doses is a proven carcinogen but the cancer rates at low doses are less well quantified, the fetus (and children in general) may be more susceptible to the carcinogenic effects of ionizing radiation than adults, and technical improvements or the use of alternate diagnostic modalities can significantly reduce fetal or postnatal exposure to diagnostic X rays.

Epidemiological Evidence Linking Childhood Cancer with Prenatal Radiation

The report of Stewart and coworkers linking elevated childhood cancer mortality in England and Wales with mothers' abdominal X-ray examinations during pregnancy was initially met with disbelief. The findings were taken more seriously when they were replicated 2 years later in an extended series and validated with radiological records (reviewed in ref. *4*). In a continuing expansion of the study, risk declined over time, from an original odds ratio (OR) of 1.91 described in 1958 to an OR of 1.39 reported in 1989 (the latter based on 15,276 case–control pairs), due to substantial reductions in the number of films per examination, the estimated fetal dose, and the use of pelvimetry. A similar elevated risk (OR = 1.47) was observed in a study in the northeastern United States, and the causality of the association was further supported by risk increases in subsequent case–control studies, including several with confirmatory radiological reports. One report described a dose–response effect for childhood cancer associated with the number of fetal X-ray exposures during the third trimester (*4*). While the increased risk estimates ranged from 20–70%, overall there was little evidence for heterogeneity among the studies. Meta-analysis calculated an overall excess of 1.38, similar to the risk of 1.39 from the large study of Stewart and coworkers (*4*), consistent with the large size and proportional contribution to the entirety of case–control data provided by the study in England and Wales. Recent Swedish and U.S. case–control studies have described lower risks, although the upper confidence limits of both are consistent with earlier risk estimates.

The risk of childhood cancer in relation to maternal abdominal diagnostic X rays has been evaluated among twins, since earlier data indicated a fivefold higher frequency of pelvimetry among twin compared to singleton births (*1*, *2*). Results from studies of twins in the large population in England and Wales, which were subsequently confirmed in Swedish and the U.S. studies, showed elevated risks of childhood cancer in association with prenatal diagnostic X-ray exposures to be similar for twins and singletons. A detailed search has not yielded evidence of confounding.

Cohort studies, ranging from less than 200 to 39,166 exposed children, have followed up the offspring of mothers who underwent diagnostic X-ray tests during pregnancy and identified 1 to 23 children who developed cancer (*1*). In a meta-analysis of 6 of the most reliable cohort studies, Doll and Wakeford calculated an overall relative risk of 1.2, not differing significantly from 1.0, but nevertheless compatible with an excess relative risk of approximately 40% as reported in the case–control studies.

In time-trend studies of childhood leukemia associated with fetal exposures to diagnostic radiation, risks declined between 1947–1957 and 1958–1960 in the northeast U.S., between 1940–1956 and 1957–1969 in England and Wales, and between 1936–1959 and 1960–1967 in Sweden, perhaps reflecting reduced use of prenatal X-ray examinations after publication of the report of Stewart *et al.* (reviewed in ref. *1*). A recent U.S. case–control study of children diagnosed with leukemia during 1989–1993 showed a decline in the proportion of subjects undergoing pelvimetry over time. The proportion of childhood leukemia cases undergoing pelvimetry has declined from 10.2% for those born in 1980 or before to 2.4% for those born in 1982–1986 and dropped further to 1.3% for those born after 1986; similarly, the corresponding proportion of controls undergoing pelvimetry has decreased from 60% for those born in 1980 or before to 2.3% for those born in 1982–1986 to 1.8% for those born after 1986 (*4*).

Controversies on Causality of Prenatal Diagnostic Radiation and Childhood Cancer Risk

The causality of the relationship of fetal diagnostic X-ray exposure to subsequent cancer risk has long been debated (*1–3*). The major argument opposing a conclusion of causation is the lack of an excess of childhood cancer among the 1,263 Japanese children exposed *in utero* to the atomic bomb explosions and followed up to age 15. Of the subset of 753 Japanese children exposed to at least 10 mGy, only two developed cancer, a 6-year-old dying of hepatoblastoma and a 14-year-old diagnosed with Wilms' tumor. Some have argued that the small number of observed cancers, particularly the absence of childhood leukemias, is inconsistent with the results of Stewart *et al.*, since the estimated doses of the Japanese survivors were larger than the fetal exposures from pelvimetry. It is possible that some of the Japanese survivors who were *in utero* at the time of the bombings could have died from leukemia before 1950, when the study of the atomic bomb survivors began. While 0.43 childhood cancer deaths were expected based on Japanese national mortality rates, 5–14 deaths were expected based on the results of Stewart *et al.* Similarly, the excess absolute risk increase estimated from the two childhood cancer cases observed was 0.7% per gray (95% CI = −0.1%–2.6% per gray), substantially less than the estimated absolute risk increase of 6% per gray derived from the study of Stewart and colleagues. Other aspects of the epidemiological and experimental literature described as inconsistent with causation included the excess risks observed for several categories of childhood cancer in addition to the leukemias, some inconsistencies within the twin studies, and the absence of increased leukemia induction after fetal irradiation in animal studies.

Cancer and Mortality Risks Linked with Newer Diagnostic Radiological Procedures

A growing number of large investigations have shown no association between ultrasound tests during pregnancy and risk of childhood leukemia. The lack of an association was consistently observed as the use of ultrasound testing rose dramatically; ultrasound examination is currently employed, often repeatedly, in substantially more than half of all pregnancies in the U.S.

The use of pediatric CT examinations has grown rapidly from the mid-1980s to the present, driven in part by technical improvements and the speed of examination made possible by the helical CT. The number of requests for CT scans in children rose 63% between 1991 and 1994, while abdominal and pelvic CT examinations increased approximately 100% from 1996 through 1999 (*5*). The use of helical CT in children reduces the need for sedation and improves the quality and precision of evaluation of the acute abdominal conditions, particularly in younger, sicker and uncooperative children. While CT examinations comprise a relatively small proportion of all diagnostic radiological examinations in children, the contribution to a child's cumulative radiation dose is substantial because of the notably higher lifetime risk per unit dose of radiation for children compared to adults. Using existing databases, Brenner and colleagues calculated age-dependent lifetime cancer mortality risks per unit dose and estimated increased lifetime risks for death from cancer of 0.18% from a CT scan of the abdomen and 0.07% from a CT scan of the head in a 1-year-old child (*5*). These risks were an order of magnitude higher than for adults receiving comparable doses.

Prospects and Problems for Future Research

While the value of additional epidemiological studies of cancer risks associated with prenatal diagnostic X-ray or ultrasound tests is unclear, it is important to quantify risks of childhood cancer in relation to CT scans. Populations that should be evaluated include children who are not chronically ill, those receiving unusually large numbers of CT scans, and those who may be unusually susceptible to radiation. Study methods should include detailed dosimetry in conjunction with validation of the numbers and types of examinations and potential confounding factors. Opportunities to evaluate cancer and other health effects in relation to CT scans may be possible in record linkage studies and the longitudinal lifetime cohort study of 100,000 children being planned by the National Institute of Child Health and Human Development, the Centers for Disease Control and Prevention, and the Environmental Protection Agency.

The current benefit of pediatric CT examinations strongly outweighs the small increase in lifetime cancer mortality. Nevertheless, technical improvements are urgently needed to reduce the radiation dose while maintaining high-quality visualization.

References

1. R. Doll and R. Wakeford, Risk of childhood cancer from fetal irradiation. *Br. J. Radiol.* **70**, 130–139 (1997).

2. B. MacMahon, Some recent issues in low-exposure radiation epidemiology. *Environ. Health Perspect.* **81**, 131–135 (1989).

3. R. H. Mole, Childhood cancer after prenatal exposure to diagnostic X-ray examinations in Britain. *Br. J. Cancer* **62**, 152–168 (1990).

4. J. F. Bithell, Epidemiological studies of children irradiated *in utero.* In *Low Dose Radiation: Biological Bases of Risk Assessment* (K. F. Baverstock and J. W. Stather, Eds.), pp. 77–87. Taylor & Francis, London, 1989.

5. D. J. Brenner, C. D. Elliston, E. J. Hall and W. E. Berdon, Estimated risks of radiation-induced fatal cancer from pediatric CT. *Am. J. Radiol.* **176**, 289–296 (2001).